

## REMARKS

This Amendment to the patent application is made in response to an Office Action dated June 29, 2005 in the file of this patent application. Reconsideration of the merits of this application, including the changes made herein, is respectfully requested.

The applicant first wishes to thank the Examiner for his courtesy in conversing with the undersigned about the merits of the Office Action in a telephone conversation of September 29, 2005. In the conversation, the undersigned asked the Examiner to discuss the Examiner's reasoning in the Office Action so that the applicant could decide an appropriate response. The Examiner indicated that one source of problem for the Examiner was the choice of the language "mutant human" referring to the protein sought to be claimed, as this language lacked definition in the Examiner's view. What the applicant has done in response above is to drop the word "mutant" to avoid any adverse implication from that word choice. The claims also all recite now that the protein is a human protein to which substitutions have been made.

In the conversation, the applicant also mentioned, but not in detail, the argument made below on the prior art rejection. The Examiner did not indicate any response on this issue.

The first ground of rejection imposed in the Office Action was under 35 USC §112, first paragraph for claim overbreadth. The applicant has responded by making changes to the claims which make it clear that what is claimed is a substituted or modified protein. Some of the claims are limited to the human protein while claim 1 is not limited in this way. The applicant has demonstrated that these specifically claimed targeted substitutions to the ribonuclease inhibitor result in a protein that is oxidation resistant. While the invention works with the human ribonuclease inhibitor, to limit the invention to the human form is too limiting. Since claims 9, 10 and 15 now are limited to the human protein and the specific substitutions that are made to the protein to result in the desired affect, and it is believed that the claims are properly subject to the rejection for overbreadth, and that this ground for rejection can be withdrawn for those claims. Arguments are presented below why the applicant believes that claim 1 is also not overbroad.

Also in the Office Action was a rejection under 35 USC §102 over a reference to Blazquez. The applicant asserts that this rejection was not proper when made but that, in any event, the reference is not relevant to the claims as they stand.

First, the applicant disagrees with the Examiner over what Blazquez teaches. In the Office Action, it states that Blazquez teaches a ribonuclease inhibitor which meets the

structural limitations of the claims. This statement, the applicant believes, is incorrect. Blazquez does teach that if one oxidizes generally all of the disulfide bonds in the porcine ribonuclease inhibitor, that the inhibitor is less binding to the ribonuclease. However, the applicant finds no teaching anywhere in the four corners of the Blazquez publication of a modified amino acid sequence for the ribonuclease inhibitor itself, nor is there a suggestion that this be done. Blazquez did oxidize the ribonuclease inhibitor molecule to reduce its binding affinity to ribonuclease, but Blazquez did this by chemically oxidizing all the disulfide bonds between any and all cysteine residues in the ribonuclease protein. This technique leaves the amino acid sequence of the protein unchanged. This approach is quite distinct from changing the amino acid sequence of the protein as the applicant has done. Not only that, but the applicant does not prevent all disulfide bond formation in the protein, only as specific defined set of disulfide bonds, those between adjacent cysteine residues. No hint is presented anywhere in Blazquez that any particular disulfide bonds are more critical to oxidation resistance than any others. Thus, this reference was not and is not a proper §102 reference against the claims of this patent application.

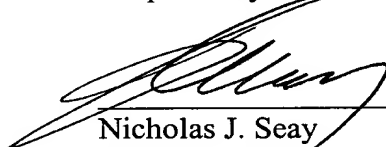
However, Blazquez is a reference and the applicant believes that the claims of the present invention are patentable over the teaching of the Blazquez paper. Again, while Blazquez teaches that disulfide bonds are important to ribonuclease inhibitor activity, it is silent as to which disulfide bonds are the important ones for this effect. Note that ribonuclease inhibitor has a large number of cysteine residues (see first paragraph of Blazquez), and there are therefore many possible sites for disruption of the disulfide bridges. By reducing the disulfide linkages chemically, Blazquez attacks all the disulfide linkages in the protein. Here, in this disclosure, specific cysteine residues are targeted for substitutions, i.e. those cysteine residues that are adjacent to other similar residues, and data are presented to demonstrate that these substitutions have the desired effect. Nothing in Blazquez suggests targeting these residues or predicts the success of this approach. Accordingly, Blazquez neither anticipates nor makes obvious the present claims of the application.

The applicant also believes that the scope of claim 1 is not overbroad. Again, the claimed invention involves targeted substitution to a specific category of cysteine residues, those adjacent to other cysteine residues. The specification includes a listing of the ribonuclease inhibitor sequences for two other species of mammal, rat and pig. As noted in the specification (page 9, paragraph starting line 4), the rat sequence has no paired cysteines, and hence the present technique is inapplicable to that protein. However, note that the pig

sequence has a pair of paired cysteine residues at locations corresponding the cysteines at 328 and 329 of the human sequence. Since this is a specific location and a specific change at this location is contemplated by the specification and claims of this application, it is asserted that these claims are not overbroad. Claim 1 has been amended so that it does not read on a ribonuclease inhibitor from a species which does not have the paired cysteine residues. The applicant has demonstrated that the substitutions at adjacent cysteine residues are sufficient to confer oxidation resistance, and this same result is entirely expected for other inhibitor proteins that share these same paired sequences, which not all of them do. Since the science supports this modest extrapolation and since the claims do not cover inhibitors which cannot be modified in the specified fashion, it is submitted that the claims as they stand are not overbroad.

Reconsideration of the merits of this patent application, and its early allowance, is respectfully requested.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'N. Seay', is written over a horizontal line.

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